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A study of microemulsion systems for transdermal delivery of triptolide

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Abstract

Triptolide possesses immunosuppressive, anti-fertility and anti-cancer activities. Due to its severe toxicity, microemulsions with controlled, sustained and prolonged delivery of triptolide via a transdermal route are expected to reduce its adverse side effects. The purpose of the present study was to investigate the microemulsions for transdermal delivery of triptolide. The pseudo-ternary phase diagrams were developed and various microemulsion formulations were prepared using oleic acid as an oil, Tween 80 as a surfactant and propylene glycol as a cosurfactant. The droplet size of microemulsions was characterized by photocorrelation spectroscopy. The transdermal ability of triptolide from microemulsions was evaluated in vitro using Franz diffusion cells fitted with mouse skins and triptolide was analyzed by high-performance liquid chromatography. The effect of menthol as a permeation enhancer, and the loading dose of triptolide in microemulsions on the permeation rate were also evaluated. The triptolide-loaded microemulsions showed an enhanced in vitro permeation through mouse skins compared to an aqueous solution of 20% propylene glycol containing 0.025% triptolide. The permeation of microemulsions accorded with the Fick's first diffusion law. No obvious skin irritation was observed for the studied microemulsion ME6, but the aqueous solution of 20% propylene glycol containing 0.025% triptolide revealed the significant skin irritation. The results indicate that the studied microemulsion systems, especially ME6, may be promising vehicles for the transdermal delivery of triptolide.

Keywords: Microemulsion; Triptolide; Transdermal delivery; Tween 80; Menthol

1. Introduction

Triptolide (Fig. 1), a purified diterpenoid triepoxide compound derived from a traditional Chinese medicine, *Tripterygium wilfordii* Hook. f. (TWHf), which is a perennial twining vine, growing densely on the shaded hill slopes in southern China. In recent years, many studies have disclosed that triptolide has various valuable functions including immunosuppressive, anti-cancer and anti-fertility activities [1–3]. The ethanol extract, ethyl acetate extract and other extracts of TWHf containing triptolide have been used for the treatment of rheumatoid arthritis and autoimmune

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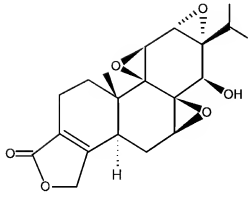

Fig. 1. The structure of triptolide.

diseases clinically and triptolide was deemed to account for the immunosuppressive activity of the extracts [4,5]. Triptolide also has been used for the treatment of rheumatoid arthritis, psoriasis and leukemia by oral or intravenous route clinically. However, the clinical uses of triptolide were limited because of its severe toxicities. The gastrointestinal adverse reactions such as nausea, vomit, bellyache, diarrhea and duodenal ulcer were always observed. Various organic systems including gastrointestinal, urogenital, cardiovascular, blood circulatory systems, bone marrow and skin, can also be affected by the systemic toxic reactions of triptolide.

Because triptolide is a moderately lipophilic and small molecule, which is clinically effective at relatively low therapeutic dose (50–200 μg/day), it is a highly appropriate agent for transdermal delivery [6]. However because of significant skin irritation at high concentration and exorbitant price of triptolide, it is very necessary to select a suitable carrier system to deliver it through skins at a relatively low dose.

Microemulsion is defined as a dispersion consisting of oil, surfactant, cosurfactant and aqueous phase, which is a single optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually within the range of 10–100 nm [7]. Microemulsions have several advantages such as enhanced drug solubility, good thermodynamic stability, ease of manufacturing and enhancement effect on transdermal ability over conventional formulations [8,9]. Recently, increasing attention has focused on microemulsions for transdermal delivery of drugs. The transdermal delivery of ketoprofen, apomorphine, estradiol and lidocaine, using microemulsions has been reported [10–14]. Several factors affecting transdermal drug delivery include the affinity of a drug to the internal phase in microemulsion, ingredients of microemulsion reducing the barrier of the stratum corneum, increased concentration gradient toward skin and the dispersed phase acting as a reservoir, which make it possible to maintain a constant concentration in continuous phase [15,16].

In transdermal delivery, the goal of dosage design is to maximize the flux through the skin into systemic circulation. A useful strategy for improving percutaneous flux is to improve the concentration of drug or choose an appropriate vehicle for the transdermal delivery [17]. However, it is hardly to enhance the permeation rate by improving the concentration of triptolide, because of severe skin irritation and exorbitant price. The microemulsion system should be a promising vehicle due to powerful ability to deliver drug through skins [18]. We previously disclosed that triptolide showed an anti-inflammatory effect on carrageenan-induced paw edema and adjuvant induced rat paw edema [19]. Therefore, the transdermal delivery of triptolide using microemulsions is expected to provide a sustained, controlled and prolonged preparation with a low toxic risk.

The aim of this work was to formulate a new microemulsion system for transdermal delivery of triptolide. The stable microemulsion systems consisting of oleic acid, Tween 80, propylene glycol and water were prepared, and its physicochemical properties, transdermal ability of triptolide and skin irritation were also evaluated.

2. Materials and methods

2.1. Materials

Oleic acid and propylene glycol were purchased from Shanghai Chemical Reagent Corporation (Shanghai, China). Tween 80 was obtained from Tianjin Bodi Chemical Company. Triptolide was obtained from Fujian Medical Sciences Institute (Fuzhou, China). Menthol was purchased from Shangai Xinhua Perfumery Factory (Shanghai, China). Other chemicals are of HPLC or analytical grade.

2.2. Construction of pseudo-ternary phase diagrams

In order to find out the concentration range of components for the existing range of microemulsions, pseudo-ternary phase diagrams were constructed using H_2O titration method at ambient temperature (25 °C). Three phase diagrams were prepared with the 1:1, 2:1 and 3:1 weight ratios of Tween 80 to propylene glycol, respectively. For each phase diagram at a specific surfactant/cosurfactant weight ratio, the ratios of oil to the mixture of surfactant and cosurfactant were varied as 0.5:9.5, 1:9, 1.5:8.5, 2:8, 2.5:7.5, 3:7, 3.5:6.5, 4:6, 4.5: 5.5, 5:5, 5.5:4.5, 6:4, 6.5:3.5, 7:3, 7.5:2.5, 8:2, 8.5:1.5, 9:1, 9.5:0.5. The mixtures of oil, surfactant and cosurfactant at certain weight ratios were diluted with H_2O dropwise, under moderate magnetic stirring. After being equilibrated, the mixtures were assessed visually and determined as being microemulsions, crude emulsions or gels. No attempt was made to distinguish between oil-in-water, water-in-oil or bicontinuous type microemulsions. Gels were claimed for those clear and highly viscous mixtures that did not show a change in the meniscus after tilted to an angle of 90°.

2.3. Preparation of microemulsions

After the microemulsion regions in the phase diagrams were identified, the microemulsion formulations were selected at different component ratios as described in Table 1. In order to prepare the drug-loaded microemulsions, a stock solution containing triptolide was prepared with the mixture of oleic acid and propylene glycol. The clear oily phase containing triptolide was obtained by diluting the weighed amount of stock solution with oleic acid and propylene glycol. Tween 80 was taken and solubilized in the distilled water. Then water was added to the clear oily phase drop by drop. The o/w microemulsions containing triptolide were obtained under a magnetic stirring at ambient temperature. Menthol as a permeation enhancer was added to the final drug-loaded microemulsion formulations at the level of 1% w/w.

Table 1
Compositions of the selected microemulsion formulations

Component	ME1	ME2	ME3	ME4	ME5	ME6	ME7
Triptolide (%)	0.025	0.025	0.025	0.025	0.010	0.025	0.050
Oleic acid (%)	1.5	1.5	6	6	6	6	6
Tween 80 (%)	20	38	20	38	20	20	20
Propylene glycol (%)	10	19	10	19	10	10	10
Water (%)	68.475	41.475	63.975	36.975	62.990	62.975	62.950
Menthol (%)	0	0	0	0	1	1	1

In order to obtain an aqueous solution of 20% propylene glycol containing 0.025% triptolide, triptolide was solubilized in an aqueous solution containing 20% propylene glycol.

2.4. Characterization of microemulsions

The pH values of microemulsions were determinated at 25 °C using a pHS-3C digital acidimeter (Shanghai Rex Instruments Factory). The viscosity of various microemulsions was measured at 25 °C using a NDJ-8S digital viscometer (Shanghai Precision and Scientific Instrument, Shanghai, China) with a No. 1 rotor set at 60 rpm. The refractive index was determinated at 25 °C using a WYA-2S digital Abbe refractometer (Shanghai Physico-optical Instrument Factory).

The average droplet size and polydispersity index of the microemulsions were determinated by photocorrelation spectroscopy using a 90 Plus instrument (Brookhaven Instruments, New York, USA) at a fixed angle of 90°. The measurement at 635 nm was obtained using a 15 mW solid state laser. Samples were suitably diluted with distilled water to avoid multi-scattering phenomena. The droplet size of the diluted microemuslions was not significantly changed. All measurements were performed at 25 °C. Each system was determinated in triplicate.

2.5. Stability of microemulsions

The chemical and physical stability of microemulsions with triptolide was studied via clarity and phase separation observation, droplet size determination and HPLC analysis of triptolide at 37 °C for up to 6 months. The concentrations of triptolide in the tested microemulsions were determinated monthly.

The centrifuge tests were also carried out to assess the physical stability of microemulsions. Microemulsions were centrifuged for 30 min at 13,000 rpm in the centrifuge tests [20].

Microemulsions were stored at 5, 15, 25 and 37 °C in the dark for 6 months, respectively. Then the clarity, phase separation and concentration of triptolide were investigated to judge the optimal storage temperature monthly.

2.6. HPLC analysis of triptolide

Triptolide was analyzed by reversed phase HPLC using Agilent 1100 series. The HPLC system consisted of quaternary pump, autosampler, diode array detector and workstation. The column was a Lichrospher C_{18} column (5 μm, 4.6 mm ID × 25 cm). The mobile phase was a methanol-0.05 mol/l potassium dihydrogen phosphate (65:35 v/v) mixture with a flow rate of 0.50 ml/min. The detection wavelength was set at 218 nm and the retention time was 9.5 min. The assay was linear ($r^2 = 0.9999$) in the concentration range of 0.07–70.0 μg/ml with a lowest detection limit at 0.015 μg/ml. The percentage recoveries ranged from 99.0 to 101.0%. No interference of the other formulation components was observed. All samples filtered through an aqueous 0.45 μm pore size membrane filter before injection.

2.7. In vitro permeation studies

The abdominal skins were obtained from male mice weighing 25 ± 2 g. After hair was removed with a depilatory, the skins were excised. The subcutaneous fat was removed, and then the skins were washed and examined for integrity. The skins were placed in a refrigerator at 4 °C overnight, and then used for the experiments. The permeation experiments were performed using a diffusion instrument (TK-12A, Shanghai, China) with a re-circulating water bath and 12 diffusion cells. The skins were clamped between the donor and the receptor chamber of vertical diffusion cells. The cell has an effective diffusional area of 2.8 cm^2 and a 7 ml cell volume. The receptor chamber was filled with freshly prepared solution of ethanol (water–ethanol 4:1 v/v) to solubilize triptolide and to ensure sink conditions. The solution of 20% ethanol was used to solubilize triptolide. The receptor chambers were thermostated at 37 °C and the solution in the receptor chambers was stirred continuously at 300 rpm. The formulations (1.5 g) containing triptolide were gently placed in the donor chamber. At 2, 4, 6, 8, 10, 12 and 24 h, 0.5 ml of the solution in the acceptor chamber was removed for HPLC determination and replaced immediately with an equal volume of fresh solution of 20% ethanol. Each sample was performed in triplicate. Cumulative corrections were made to obtain the total amount of triptolide permeated at each time interval.

The cumulative amount of triptolide permeated through mouse skins was plotted as a function of time. The permeation rate of triptolide at steady-state (J_s, μg/cm^2 per h) through mouse skin was calculated from the slope of linear portion of the cumulative amount permeated through the mouse skins per unit area versus time plot [21].

In order to obtain the permeability coefficient K_p (cm/h), we used the equation:

$$K_p = J_s / C_0,$$

where K_p is the permeability coefficient, J_s is the flux calculated at steady-state and C_0 represents the drug concentration which remains constant in the vehicle.

2.8. Skin irritation studies

ME6 and the aqueous solution containing 0.025% triptolide were selected as the tested formulations for skin irritation studies. All samples were applied to the shaved skin on the back of six New Zealand rabbits, and then the rabbits were secured. On one side of the back, a control microemulsion and aqueous solution (without any drug) and on another side ME6 and the aqueous solution containing 0.025% triptolide were applied for each day. The animals were observed and evaluated for any sign of erythema or oedema for a period of 7 days [22].

2.9. Statistical analysis

All skin permeation experiments were repeated three times and data were expressed as the mean value ± S.D. Statistical data were analyzed by one-way analysis of variance (ANOVA). A multiple comparison test was used to compare different formula-

tions, and a P value of 0.05 was considered to be significant.

3. Results and discussion

3.1. Phase studies

The studied systems composed of safe constituents including oleic acid, propylene glycol, Tween 80 and water. The construction of phase diagrams makes it easy to find out the concentration range of components for the existence range of microemulsions. The pseudo-ternary phase diagrams with various weight ratios of Tween 80 to propylene glycol are described in Fig. 2. The translucent microemulsion region is presented in phase diagrams. No distinct conversion from water-in-oil (w/o) to oil-in-water (o/w) microemulsions was observed. The gel area shows the transparent and high viscosity region. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual observation. No liquid crystalline structure was observed using cross polarizer. The area of microemulsion isotropic region changed slightly in size with the increasing ratio of surfactant to cosurfactant. A similar result was obtained from an ethyl laurate-based microemulsion system with Tween 80 as surfactant, propylene glycol and ethanol as cosurfactant [23].

3.2. Preparation and characterization of microemulsions

Various microemulsions were selected from the 2:1 phase diagram. Tween 80 was added into oily phase in the construction of phase diagrams. A relatively long time (about 2–3 h) was required to obtain transparent microemulsions under magnetic stirring when microemulsions contained 20% Tween 80, 10% propylene glycol and 6% oleic acid. However, when Tween 80 was solubilized into aqueous phase, and then the aqueous phase was added to oily phase containing propylene glycol and oleic acid, the clear microemulsions could be quickly obtained. But the order of the addition of Tween 80 did not change the physicochemical properties of the microemulsions. So in order to reduce the equilibrium time, Tween 80 was added to water in preparation of drug-loaded microemulsions.

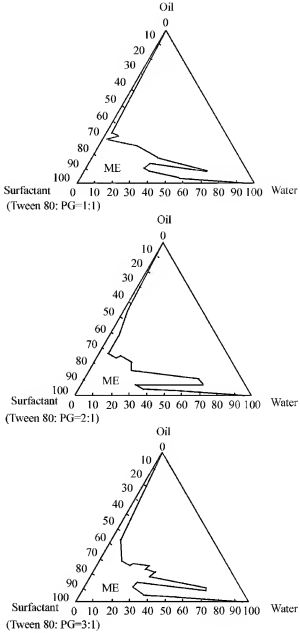

Fig. 2. Pseudo-ternary phase diagrams of the oil-surfactant-water system at 1:1, 2:1, and 3:1 weight ratios of Tween 80 to propylene glycol at 25 °C. ME represents microemulsion regions).

In addition, the influence of the order of the addition of propylene glycol on the preparation of microemulsions was also studied. When Tween 80 was added to aqueous phase, and propylene glycol was added to oily phase or aqueous phase, no change in the equilibrium time and the physicochemical properties was

observed. It does not accord with the result obtained by Vandamme [24], namely the order of the addition of cosurfactant could influence the time required to receive equilibrium. It may be due to quick distribution of propylene glycol between oily phase and aqueous phase. It is concluded that the order of the addition of this surfactant should be a very important factor for the preparation of microemulsions.

The physico-chemical parameters of microemulsions are reported in Table 2. The ME1 containing 1.5% oil, 20% Tween 80 and 10% propylene glycol had the lowest average droplet size, viscosity and refractive index. It is obvious that the average droplet size, viscosity and refractive index of microemulsions with more oil and surfactant increased significantly. The pH values were within the physiological range. The droplet size of all microemulsions ranged from 10 to 150 nm and 90% of the droplets had small droplet size < 100 nm. The average droplet size of ME3 containing triptolide was 59.8 nm. However the average droplet size and polydispersity of microemulsion in the absence of triptolide, were only 23.1 ± 0.6 and 0.258 ± 0.006 nm, respectively. In addition, the incorporation of 1% menthol to ME3 resulted in an 11.3 nm increase of the average droplet size, but no change in viscosity and refractive index of microemulsions was observed. The increase of the average droplet size of microemulsion may be related to the embedding of triptolide and permeation enhancer in the interfacial film [14,25].

3.3. Stability of microemulsions

All microemulsion formulations were stable at 37 °C in the presence or absence of triptolide. The changes of particle size, phase separation and degradation of triptolide were not observed during 6 months. The centrifuge tests showed that all microemulsions had good physical stability.

Microemulsions stored at 15, 25 and 37 °C showed no change in clarity and phase behavior. The concentrations of triptolide in microemulsions were almost constant and no degradation was observed. But the phase separation and turbidity were observed for microemulsions at 5 °C. The coagulating of the internal phase might lead to this instability. But these microemulsions were easily recovered by heating up. So microemulsions should be kept above 15 °C at least.

A long-term storage of triptolide in an aqueous environment may result in a potential tendency of hydrolysis, because triptolide has unstable ether-bond. Therefore, it is disadvantageous that triptolide was formulated to an aqueous environment. The rate of hydrolysis of triptolide is also influenced significantly by pH value. Especially when pH value is less than 3 or more than 8, the hydrolysis of triptolide can be promoted. However, when the pH value is ranging from 4 to 6, the hydrolysis can be inhibited [26]. All microemulsions had appropriate pH values and triptolide was incorporated into the oily phase of microemulsions and avoided the contact with water in external phase. The hydrolysis of triptolide in microemulsions was not detected during 6 months. It is likely that microemulsion provided an inert circumstance and appropriate pH value for triptolide. Therefore, triptolide in microemulsions was protected from degradation effectively.

3.4. In vitro permeation studies

The percutaneous permeation parameters of the tested microemulsion formulations were presented in Table 3. The permeation profiles of triptolide through

Table 2
Physicochemical characterization of microemulsions in the presence of triptolide

Microemulsion	Diameter (nm)	Polydispersity	Viscosity (mPa·S)	pH	Refractive index
ME1	12.7 ± 1.6	0.220 ± 0.014	13.5 ± 0.8	5.73 ± 0.04	1.3682
ME2	30.8 ± 3.1	0.338 ± 0.028	432.4 ± 0.7	6.58 ± 0.03	1.4039
ME3	59.8 ± 1.1	0.145 ± 0.012	104.0 ± 0.5	5.35 ± 0.03	1.3802
ME4	81.5 ± 0.2	0.352 ± 0.012	722.0 ± 0.8	5.94 ± 0.02	1.4124
ME5	53.7 ± 1.5	0.165 ± 0.006	103.5 ± 0.5	5.35 ± 0.03	1.3801
ME6	71.1 ± 1.7	0.197 ± 0.001	104.0 ± 0.4	5.35 ± 0.03	1.3813
ME7	82.7 ± 1.9	0.210 ± 0.011	104.3 ± 0.6	5.35 ± 0.03	1.3815

Table 3
Percutaneous permeation parameters of the tested vehicles

Vehicles	J_s (μg/cm^2 per h)	K_p ($\times 10^3$ cm/h)
ME1	1.51 ± 0.15**	6.04 ± 0.60**
ME2	0.61 ± 0.08	2.44 ± 0.32
ME3	1.58 ± 0.12**	6.32 ± 0.48**
ME4	0.98 ± 0.06*	3.92 ± 0.24*
ME5	0.81 ± 0.09	3.24 ± 0.36
ME6	2.08 ± 0.10**	8.32 ± 0.40**
ME7	4.18 ± 0.12**	16.72 ± 0.48**
The aqueous solution	0.89 ± 0.07	3.56 ± 0.28

*$P<0.05$, **$P<0.01$ compared with the aqueous solution of 20% propylene glycol containing 0.025% triptolide.

mouse skins from various vehicles are shown in Figs. 3 and 4. A steady increase of triptolide in the receptor chambers with time was observed. The permeation profiles of microemulsions followed zero order release kinetics. Statistical comparison of the flux throughout 24 h showed that most of the microemulsions provided fluxes ($P<0.05$) higher than the aqueous solution containing 0.025% triptolide. Fig. 3 shows that the permeated amounts of triptolide from the different vehicles, except ME2, were no difference before 10 h. However, significant difference between microemulsions and the aqueous solution was observed at the end of experiments. And the permeation flux from the aqueous solution decreased significantly after 10 h. This revealed that the inability of the aqueous solution to provide prolonged delivery of triptolide. This phenomenon may be a result of the depletion of the driving concentration in the donor chamber.

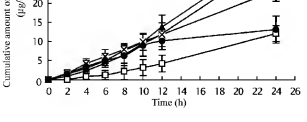

Fig. 3. Permeation profiles of triptolide through mouse skins from the microemulsions and the aqueous solution. ME1 (◇), ME2 (□), ME3 (▲), ME4 (×), the aqueous solution (●).

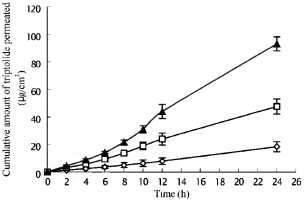

Fig. 4. The effect of the loading dose of triptolide in microemulsions on the permeation rate. ME5 (◇), ME6 (□), ME7 (▲).

ME1 and ME3 containing a lower amount of Tween 80 and propylene glycol, provided higher flux ($P<0.05$) than ME2 and ME4, respectively. The content of surfactant mixture in microemulsions affected the skin permeation flux of triptolide significantly. This may be due to an increased thermodynamic activity of the drug in microemulsions at the lower concentration of surfactant and cosurfactant [10]. The thermodynamic activity of drug in the formulation is a significant driving force for the release and penetration of the drug into skin [27]. The thermodynamic driving force for release reflects the relative activities of the drug in different phases [15]. Since drug can be released from the internal phase to external phase and then from the external phase to the skin, the relative activities may monitor the skin permeation flux. In addition, the surfactant and cosurfactant may exist in each phase, so triptolide can partly solubilize in external phase. The depletion of triptolide in external phase because of the permeation into the skin can be supplemented by the release of triptolide from internal phase. Then the zero order release kinetics and sustained, controlled, prolonged delivery of triptolide were obtained. This may also be the main mechanism of permeation of triptolide into the skin from these microemulsions.

Passive permeation of drug across the skin can be increased with transdermal permeation enhancer that can remove reversibly the barrier resistance. The enhancers can increase the transport through skin by modifying the diffusion or partition coefficient of drug [28]. Oleic acid is also considered as a powerful

permeation enhancer, but the data presented in Table 3 shows that ME3 with a high concentration of oleic acid did not result in a significant enhancement compared to ME1. It is concluded that oleic acid was difficult to penetrate into corneum stratum because of the encapsulation of surfactant and cosurfactant [25]. Ideally, an effective permeation enhancer should cause minimal tissue damage and toxicity, especially for a chronic application. Menthol is a monocyclic terpene with a pleasant taste and odor. It is widely consumed as a flavoring agent in oral dosage forms and as a fragrance with a mild antipruritic effect in topical formulations [29]. Due to the pleasant taste associated with menthol, its use in transdermal drug delivery system may increase patient acceptability. The effect of menthol on transdermal absorption of several drugs has been reported [30]. Significant skin permeation enhancing effect was observed in this experiment. When 1% menthol was incorporated into ME3, the permeation rate of triptolide increased from 1.58 ± 0.04 to 2.08 ± 0.06 μg/cm^2 per h ($P < 0.05$). So menthol as a fragrance and permeation enhancer is a very suitable agent for the triptolide-loaded microemulsion.

The effect of the loading dose of triptolide in microemulsions on the permeation rate is shown in Fig. 4. Increasing the loading dose is well known to be an effective method to improve the skin permeation rate of various compounds [31]. With 1% menthol in each formulation as an enhancer, the permeation rate of triptolide increased from 0.81 ± 0.09 to 4.18 ± 0.12 μg/cm^2 per h when the loading dose of triptolide increased from 0.01 to 0.05%. The permeation rate of triptolide was almost linearly improved as a function of loading dose and the permeation of microemulsions accorded with the Fick's first diffusion law.

A high loading dose of triptolide can lead to an increased flux, but the wastage of costly triptolide and its potential toxic effect should be considered. The effect of triptolide on skin irritation was studied by Lin and the result showed that aqueous solution containing 400 μg/ml of triptolide could induce obvious erythema and edema on both intact and injured skins of rabbits [32]. The previous investigation about microemulsions with 0.025% triptolide validated the anti-inflammatory activity [19]. Therefore, the suitable concentration of triptolide in microemulsions should be 0.025%. In the previous work, all the microemulsion formulations contained a large amount of surfactants and isopropyl myristate with a powerful ability to perturb the stratum corneum. Furthermore, the best formulation consisting of 40% isopropyl myristate, 50% Tween 80/propylene glycol (5:1) and water is a w/o type of microemulsion. Triptolide dissolved in outer phase of w/o microemulsion might directly contact with the surface of skin. It is not suitable for long-term use from the point of view of safety. Therefore, the formulation of ME6 should be more valuable for the further exploration.

3.5. Skin irritation studies

The irritation studies did not show visible irritation after application of ME6 for 7 days on the skin of rabbits. No erythema or oedema was observed on the skin of rabbits for ME6. Only rubefaction appeared on the skins of some rabbits occasionally on the third or fourth day and disappeared on the sixth or seventh day. However, the aqueous solution containing 0.025% triptolide induced significant erythema and edema. The encapsulation of microemulsion might reduce the skin irritation induced by triptolide. This microemulsion system for the transdermal delivery of triptolide is viable.

4. Conclusions

The microemulsions containing triptolide were studied for transdermal delivery. The different microemulsion formulations were selected using the pseudo-ternary phase diagrams. The order of the addition of Tween 80 is a very important factor for the preparation of microemulsions. The incorporation of triptolide and menthol into microemulsions led to a significant increase of droplet size due to their location in interfacial film. The in vitro permeation studies showed that microemulsions with lower content of surfactant mixture could increase the transdermal ability. Menthol as a permeation enhancer could significantly increase the in vitro permeation rate of triptolide through mouse skins. The triptolide-loaded microemulsions showed the controlled, sustained and prolonged delivery when compared with an aqueous solution of 20% propylene glycol containing 0.025%

triptolide. The permeation rates of triptolide from microemulsions accorded with the Fick's first diffusion law. The triptolide-loaded microemulsion system (ME6) reduced the skin irritation induced by triptolide compared to the aqueous solution of 20% propylene glycol with 0.025% triptolide.

Acknowledgements

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